

Middle cerebral artery blood velocity is reduced with hyperthermia during prolonged exercise in humans

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1. In the present study we examined the effect of hyperthermia on the middle cerebral artery mean blood velocity (MCA V_{mean}) during prolonged exercise. We predicted that the cerebral circulation would be impaired when hyperthermia is present during exercise and assumed that this could be observed as a reduced MCA V_{mean} .
2. Eight endurance trained men (maximum oxygen uptake ($\dot{V}_{\text{O}_{2,\text{max}}}$) $70 \pm 1 \text{ ml min}^{-1} \text{ kg}^{-1}$ (mean \pm S.E.M.)) performed two exercise trials at 57 % of $\dot{V}_{\text{O}_{2,\text{max}}}$ on a cycle ergometer in a hot (40 °C; hyperthermic trial) and in a thermoneutral environment (18 °C; control trial). In the hyperthermic trial, the oesophageal temperature increased throughout the exercise period reaching a peak value of 40.0 ± 0.1 °C at exhaustion after 53 ± 4 min of exercise. In the control trial, exercise was maintained for 1 h without any signs of fatigue and with core temperature stabilised at 37.8 ± 0.1 °C after ~ 15 min of exercise.
3. Concomitant with the development of hyperthermia, MCA V_{mean} declined by 26 ± 3 % from $73 \pm 4 \text{ cm s}^{-1}$ at the beginning of exercise to $54 \pm 4 \text{ cm s}^{-1}$ at exhaustion ($P < 0.001$). In contrast, MCA V_{mean} remained unchanged at 70–72 cm s^{-1} throughout the 1 h control trial.
4. When individually determined regression lines for MCA V_{mean} and arterial carbon dioxide pressure ($P_{\text{a,CO}_2}$) obtained during preliminary exercise tests were used to account for the differences in $P_{\text{a,CO}_2}$ between the hyperthermic and control trial, it appeared that more than half of the reduction in MCA V_{mean} (56 ± 8 %) was related to a hyperventilation-induced drop in $P_{\text{a,CO}_2}$. Declining cardiac output and arterial blood pressure accounted for the remaining part of the hyperthermia-induced reduction in MCA V_{mean} .
5. The present results demonstrate that the development of hyperthermia during prolonged exercise is associated with a marked reduction in MCA V_{mean} .

The combination of exercise and environmental heat stress is believed to result in competition between exercising muscles, skin compartments and other tissues for the available systemic blood flow (Rowell, 1974, 1986; Nielsen *et al.* 1990). Several studies have shown that hyperthermia induces an increase in skin blood flow, while splanchnic, renal and in some cases muscle blood flow is reduced (Rowell *et al.* 1965; Johnson & Rowell, 1975; Rowell, 1986; González-Alonso *et al.* 1998). However, it is not known if cerebral blood flow is affected when environmental heat stress is also present during exercise. In awake resting baboons cerebral blood flow is unaffected by hyperthermia (Hales *et al.* 1979) and it has been suggested that cerebral blood flow in humans would also remain unaltered, except if hyperthermia-induced hyperventilation induces a drop in $P_{\text{a,CO}_2}$ (Rowell, 1986). Yet, in exercising as well as resting humans, hyperthermia is often accompanied by an increase in ventilation (Haldane, 1905; Rowell *et al.* 1969; Cabanac &

White, 1995; González-Alonso *et al.* 1998), resulting in a reduced $P_{\text{a,CO}_2}$ (González-Alonso *et al.* 1998), and as $P_{\text{a,CO}_2}$ has a strong influence on the cerebral circulation (Heistad & Kontos, 1983), blood flow could be reduced during exercise with hyperthermia. Furthermore, severe hyperthermia can induce a reduction in cardiac output during exercise (Rowell *et al.* 1966; González-Alonso *et al.* 1999b), and an insufficient increase in systemic blood flow was found to reduce the cerebral blood velocity during exercise with a large muscle mass (Ide *et al.* 1998).

When exercise is performed in normal environmental temperatures, regional cerebral blood flow increases (Huang *et al.* 1991, 1992; Jørgensen *et al.* 1992; Hellström *et al.* 1996), although flow to the whole brain may not be affected (Madsen *et al.* 1993; Jørgensen, 1995). Transcranial Doppler-detected blood velocity in the major cerebral arteries is a reflection of the changes in blood flow to single vessels; thus during cycling, blood velocity in both the anterior cerebral artery and

especially the middle cerebral artery are enhanced bilaterally (Jørgensen *et al.* 1992; Linkis *et al.* 1995). Transcranial Doppler ultrasound has the advantage of being a non-invasive technique for evaluation of cerebral perfusion with the possibility of continuous, real-time recording. On the other hand, a major limitation of transcranial Doppler ultrasound is that any changes in the cross-sectional area of the insonated vessel will lead to a disproportional relationship between cerebral blood velocity and cerebral blood flow. Controversy exists within this area (Poulin *et al.* 1999; Giller *et al.* 2000) and different cardiovascular responses may influence cerebral artery velocity differently. However, Serrador *et al.* (2000) recently found a high correlation between relative changes in cerebral blood velocity and changes in cerebral blood flow over a wide range of flow velocities, and therefore it seems that transcranial Doppler determination of blood velocity can provide a useful indication of the real changes in the underlying cerebral blood flow.

Taken together, these observations indicated to us that the cerebral circulation might be substantially affected by hyperthermia during prolonged exercise, and we expected that this would be reflected in the transcranial Doppler-detected blood velocity in the major cerebral arteries. To test this hypothesis, we therefore determined the middle cerebral artery mean blood velocity (MCA V_{mean}) during prolonged exercise with and without hyperthermia.

METHODS

Subjects

The eight endurance trained male cyclists participating in this study had a mean age of 23 ± 1 years (mean \pm S.E.M.), height of 177 ± 3 cm, body weight of 66 ± 2 kg, maximum oxygen uptake ($\dot{V}_{\text{O}_{2,\text{max}}}$) of 70 ± 1 ml min⁻¹ kg⁻¹ and maximum heart rate of 189 ± 2 beats min⁻¹. The experiments were carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Copenhagen and Frederiksberg (KF 01-135/00). Written informed consent was obtained from the participants.

Experimental design

On two occasions separated by 1–6 days, subjects exercised continuously on a cycle ergometer (Monark 829E) at a power output (198 ± 10 W, 80–90 r.p.m.) that initially elicited $\sim 57\%$ of $\dot{V}_{\text{O}_{2,\text{max}}}$. In the hyperthermic trial, subjects cycled in an uncompensatory hot environment (40°C, 20% relative humidity; $E_{\text{req}}/E_{\text{max}} = 1.2$, where E_{req} is the evaporation required for heat balance and E_{max} is the calculated maximum evaporation capacity) until volitional exhaustion, while the control trial was carried out in a thermoneutral environment (18°C, 40% relative humidity). The treatment order was randomly assigned and counterbalanced across subjects. To avoid differences in the degree of dehydration between the two trials, subjects drank 0.8 ± 0.2 l of pre-warmed water (adjusted to the core temperature) in the hyperthermic trial and 0.3 ± 0.1 l in the control trial. This resulted in a similar level of body weight loss at the end of the two trials ($0.7 \pm 0.1\%$ in the control and $0.7 \pm 0.2\%$ in the hyperthermic trial).

Subjects arrived at the laboratory ~ 1 h before the start of the experiment. Upon arrival, they rested in a thermoneutral room and an oesophageal thermocouple was inserted, and an ultrasound

Doppler probe and a heart rate (HR) monitor were attached to the subjects. The subjects then entered the climatic chamber, were weighed and sat quietly on the ergometer for 10 min while resting measurements were obtained.

During exercise, MCA V_{mean} , HR and core temperature were recorded continuously. Blood pressure and pulmonary measurements were made every 10 min, while cardiac output was measured in triplicate over 10 min periods beginning at 5 and at 40 min of exercise. Body weight was recorded immediately after exercise.

Oxygen consumption and cardiac output

Pulmonary oxygen consumption (\dot{V}_{O_2}), carbon dioxide elimination (\dot{V}_{CO_2}), ventilation (\dot{V}_E), end-tidal partial pressure of O₂ (P_{ET,O_2}) and end-tidal partial pressure of CO₂ ($P_{\text{ET},\text{CO}_2}$) were measured on-line with a metabolic cart (model CPX/D, MedGraphics, St Paul, MN, USA). Arterial partial pressure of CO₂ (P_{a,CO_2}) was calculated using the formula from Jones *et al.* (1979), which corrects for differences between end-tidal and arterial partial pressure of CO₂ (P_{CO_2}). Cardiac output was measured in triplicate using the CPX/D computerised version of the CO₂-rebreathing technique of Collier (1956) and these measurements were also corrected for differences between $P_{\text{ET},\text{CO}_2}$ and P_{a,CO_2} (Jones *et al.* 1979). A tight correlation between $P_{\text{ET},\text{CO}_2}$ and P_{a,CO_2} as well as between the estimated mixed venous P_{CO_2} and femoral P_{CO_2} was recently established in our laboratory under similar exercise conditions (González-Alonso *et al.* 1998). Heart rate was recorded with a Polar Vantage NV (Polar Electro; sampling rate 5 s) and stroke volume was calculated by dividing cardiac output by heart rate. Systolic and diastolic blood pressure were measured in duplicate on the left arm by the auscultatory method using an inflatable Riva-Rocci cuff. Mean arterial pressure (MAP) was calculated as $((2 \times \text{diastolic pressure}) + \text{systolic pressure})/3$.

Middle cerebral blood velocity

The MCA V_{mean} was determined with transcranial Doppler ultrasound (Transcan, EME, Überlingen, Germany). The proximal segment of the MCA was insonated at a depth of 45–50 mm from the temporal bone depending on the position with the best signal–noise ratio (Aaslid *et al.* 1982). The probe was secured with a customised headband and the position was maintained throughout the examination. Identical repositioning of the probe on the subsequent exercise trial was attempted by measuring the distance from the middle of the ear and the lateral corner of the eye to the probe. We also attempted to maintain the same angle of insonation for all measurements, and reproducibility of the repositioning of the probe was assessed by comparing the resting V_{mean} values (see Fig. 1A). MCA V_{mean} was computed as the time-average of continuously sampled maximum frequency Doppler shifts for each heart beat which afterwards were averaged over 1 min periods every 5 min. Furthermore, MCA V_{mean} values obtained in the hyperthermic trial were related to the P_{a,CO_2} of the control trial using individually determined regression lines for MCA V_{mean} and P_{a,CO_2} obtained during exercise. The linear regression lines ($r^2 = 0.92$ – 0.99) were made on the basis of four pairs of related MCA V_{mean} and P_{a,CO_2} values, and the slopes of the regression line were used to express the 'CO₂ reactivity'. P_{a,CO_2} values in the range from ~ 30 to ~ 45 mmHg were established in preliminary exercise tests by the subjects either hypo- or hyperventilating. The subjects were provided with auditory feedback on their breathing efforts, and the target levels of P_{a,CO_2} were attained after ~ 1 min and then maintained for an additional minute while measurements were made. To reduce the influence from non-linear curves, data for the regression lines included only values just outside the P_{a,CO_2} range for each subject (P_{a,CO_2} range in hyperthermic trial). The 'CO₂ reactivity' determined during exercise was 2.3 ± 0.1 cm s⁻¹ mmHg⁻¹ or $3.4 \pm 0.3\%$ mmHg⁻¹, which is similar to the 'CO₂ reactivity' reported at rest (Jørgensen, 1995).

In one subject, V_{mean} was measured both in the MCA and in the contralateral anterior cerebral artery (ACA) with blood velocity in both arteries showing the same pattern of response to hyperthermia (see Table 2).

Oesophageal temperature (T_{oes}) was measured with a thermocouple (model MOV-A, Ellab) inserted through the nasal passage to a distance equal to one-quarter of the subjects' standing height. Room air temperature was measured with another thermocouple (A-H3, Ellab), and both thermocouples were connected to a recorder (CTF 9008 precision thermometer, Ellab) interfaced to an IBM computer and temperatures were recorded every 15 s with an accuracy of 0.1 °C.

Statistical analysis

One- and two-way (time-by-trial) repeated measures analysis of variance (ANOVA) was performed to evaluate differences between and within trials. Following a significant F test, differences between pairs were identified using Tukey's honestly significance (HSD) *post hoc* procedure. Stepwise forward regression analysis was also used to test the strength of the association between MCA V_{mean} , ventilation and oesophageal temperature. The significance level was set at $P < 0.05$. Data are presented as means \pm S.E.M. unless otherwise indicated.

RESULTS

Oesophageal temperature (T_{oes}) and body weight were similar prior to the trials (mean range between trials, 36.9–37.0 °C and 66.2–66.3 kg, respectively). In the hyperthermic trial T_{oes} increased throughout the exercise period and was significantly higher than control after 10 min of exercise. Exhaustion occurred after 53 ± 4 min of exercise in the hyperthermic trial and coincided with a T_{oes} of 40.0 ± 0.1 °C (see Fig. 2A). In the control trial, exercise was maintained for 1 h without any signs of fatigue and with core temperature stabilising at 37.8 ± 0.1 °C after 15 min of exercise.

Ventilatory response

Oxygen consumption was similar in the two trials and remained fairly constant over time (2.6 ± 0.1 l min⁻¹ in both trials). During the hyperthermic trial, \dot{V}_{E} increased progressively over time from 58.7 ± 3.4 l min⁻¹ at 10 min to 83.6 ± 3.4 l min⁻¹ at exhaustion ($P < 0.001$; Fig. 1C) and \dot{V}_{CO_2} increased in the same period from 2.3 ± 0.1 l min⁻¹ to 2.5 ± 0.1 l min⁻¹ ($P < 0.001$). Concomitant with the increase in \dot{V}_{CO_2} and \dot{V}_{E} , $P_{\text{ET,CO}_2}$ and the calculated $P_{\text{a,CO}_2}$ decreased from 44.9 ± 0.8 and 40.9 ± 0.5 mmHg to 38.6 ± 0.6 and 36.0 ± 0.5 mmHg respectively ($P < 0.001$; Fig. 1B and Table 1). Furthermore, $P_{\text{ET,O}_2}$ increased from 97.2 ± 1.7 mmHg at 10 min to 105.3 ± 1.5 mmHg at exhaustion ($P < 0.001$). In the control trial, all ventilatory variables were not significantly changed over time (10–60 min) and the values were of similar magnitude to the values at 10 min in the hyperthermic trial.

Cardiovascular responses

MCA V_{mean} was similar at rest before the two trials (58.4 ± 4.2 cm s⁻¹ before the control trial *vs.* 58.2 ± 4.3 cm s⁻¹ before the hyperthermic trial). In both trials MCA V_{mean} increased at the onset of exercise, and in the control trial it remained elevated at 70–72 cm s⁻¹

throughout the exercise period (Fig. 1A). In contrast, during the hyperthermic trial, MCA V_{mean} decreased from 72.7 ± 3.8 cm s⁻¹ at the beginning of exercise to 54.4 ± 4.3 cm s⁻¹ during the last 5 min of exercise ($P < 0.001$; Fig. 1A). When the hyperthermic trial MCA

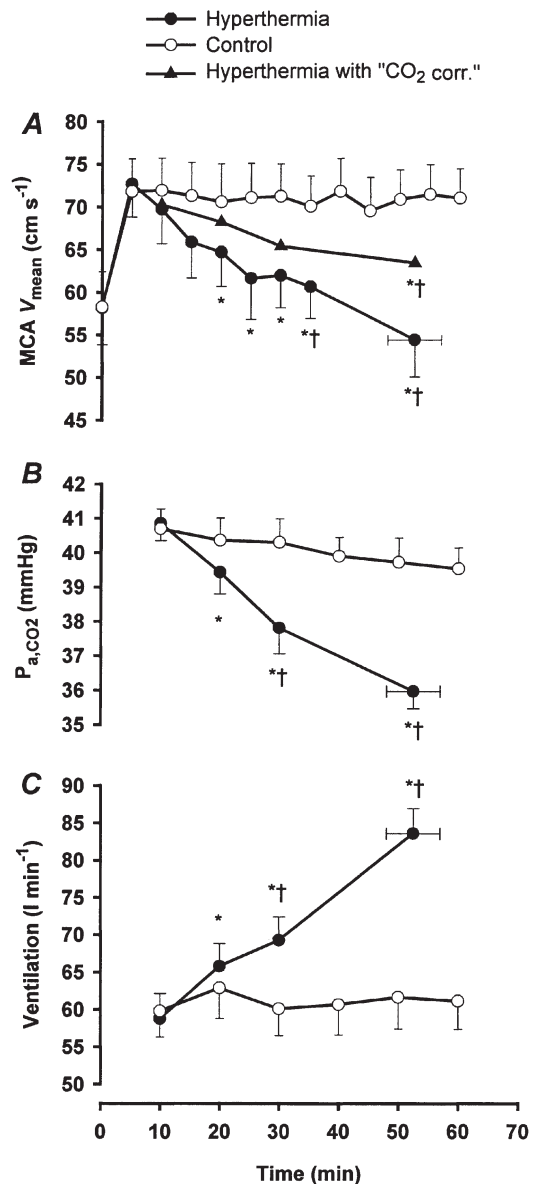


Figure 1. Middle cerebral artery mean blood velocity, arterial carbon dioxide pressure and ventilation during prolonged exercise with and without hyperthermia

A, MCA V_{mean} (middle cerebral artery mean blood velocity) during prolonged exercise in control (○), during hyperthermia (●) and in the when the values were 'corrected' and related to the $P_{\text{a,CO}_2}$ in the control trial (▲). B, $P_{\text{a,CO}_2}$ (calculated arterial carbon dioxide pressure) in control (○) and during hyperthermia (●). C, ventilation in control (○) and during hyperthermia (●). Values are means \pm S.E.M. for 8 subjects. * Significantly different from 10 min value, $P < 0.05$; † significantly different from control, $P < 0.05$.

Table 1. Rating of perceived exertion, ventilatory and cardiovascular responses during prolonged submaximal exercise with and without hyperthermia

	Time (min)	RPE	\dot{V}_{O_2} (l min ⁻¹)	\dot{V}_{CO_2} (l min ⁻¹)	P_{ET,CO_2} (mmHg)	P_{ET,O_2} (mmHg)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Control trial	10	10 ± 1	2.63 ± 0.12	2.41 ± 0.11	44.8 ± 0.9	98.7 ± 1.0	163 ± 2	66 ± 3
	20	11 ± 1	2.63 ± 0.11	2.38 ± 0.11	44.6 ± 0.9	98.9 ± 1.1	164 ± 2	65 ± 2
	30	12 ± 1	2.64 ± 0.11	2.37 ± 0.10	44.2 ± 0.9	98.5 ± 0.9	164 ± 2	64 ± 2
	40	12 ± 1	2.63 ± 0.13	2.35 ± 0.11	43.6 ± 0.9	98.8 ± 0.9	164 ± 2	63 ± 2
	50	12 ± 1	2.61 ± 0.12	2.38 ± 0.11	43.7 ± 1.0	98.5 ± 1.4	165 ± 2	63 ± 2
	60	12 ± 1	2.61 ± 0.11	2.34 ± 0.10	43.2 ± 0.8	99.1 ± 0.8	165 ± 2	63 ± 2
Hyperthermic trial	10	13 ± 1	2.56 ± 0.11	2.34 ± 0.10	44.9 ± 0.8	97.2 ± 1.7	162 ± 3	66 ± 2
	20	14 ± 1	2.59 ± 0.10	2.39 ± 0.10	43.4 ± 0.7*	99.9 ± 1.5	159 ± 2	64 ± 2
	30	16 ± 1	2.60 ± 0.11	2.40 ± 0.10	41.0 ± 1.1*†	101.7 ± 1.4*†	159 ± 3	60 ± 2*†
	53 ± 4	20 ± 0	2.63 ± 0.10	2.51 ± 0.11*†	38.6 ± 0.6*†	105.3 ± 1.5*†	156 ± 3*†	57 ± 2*†

Values are means ± S.E.M. for 8 subjects. RPE, rating of perceived exertion; P_{ET,CO_2} , end-tidal CO_2 pressure; P_{ET,O_2} , end-tidal O_2 pressure. The final point in the hyperthermic trial (53 ± 4 min) is the average time to exhaustion (range 37–59 min). *Significantly different from 10 min value, $P < 0.05$; †significantly different from control, $P < 0.05$.

Table 2. Individual cardiovascular responses during prolonged submaximal exercise with and without hyperthermia

Subject	Cardiac output (l min ⁻¹)				MCA V_{mean} (cm s ⁻¹)			
	HY		CON		HY		CON	
	Start	End	Start	End	Start	End	Start	End
JT	21.8	20.4	21.3	21.8	67.7	49.9	68.1	67.6
MT	20.2	18.7	19.6	19.6	81.4	64.3	81.6	76.1
PR	17.9	15.9	17.9	17.9	60.5	48.0	54.8	55.3
LT	19.3	19.2	19.3	19.3	78.6	58.8	81.2	79.6
CA	18.6	17.4	18.1	17.8	55.1	30.1	60.0	56.0
MH	17.0	15.7	15.7	15.8	73.8	53.2	79.6	75.9
GR	23.1	21.9	22.3	23.4	87.3	69.5	82.4	81.9
LN	19.9	18.5	19.1	19.3	76.9	61.2	66.5	68.4
Mean	19.7 ± 0.8	18.5 ± 0.9	19.2 ± 0.2	19.4 ± 0.8	72.7 ± 3.8	54.4 ± 4.3	71.8 ± 3.8	70.1 ± 3.6

Individual and average values of cardiac output and MCA V_{mean} obtained at the start and end of the hyperthermic (HY) and control (CON) trial. In subject GR, V_{mean} was also measured in the contralateral anterior cerebral artery, and during the hyperthermic trial V_{mean} decreased from 45.6 cm s⁻¹ after 5 min of exercise to 36.9 cm s⁻¹ at the end of exercise. Average values are means ± S.E.M. for 8 subjects. See also Figs 1 and 2.

V_{mean} values were ‘corrected’ for the differences in P_{a,CO_2} (Fig. 1A; ▲, hyperthermia with ‘ CO_2 correction’) between trials it appeared that 56 ± 8% of the reduction in MCA V_{mean} was related to the concomitant decrease in P_{a,CO_2} (Fig. 1A and B). However, the ‘ CO_2 corrected’ value of MCA V_{mean} at exhaustion remained significantly lower than the value in the control trial (63.4 ± 3.8 *vs.* 71.0 ± 3.5 cm s⁻¹, $P < 0.05$; Fig. 1A).

At the beginning of exercise, cardiac output was slightly elevated in the hyperthermic trial compared to control (19.7 ± 0.8 l min⁻¹ *vs.* 19.2 ± 0.8 l min⁻¹; $P < 0.05$). This pattern was reversed at the end of exercise, where cardiac output in the hyperthermic trial declined to 18.5 ± 0.9 l min⁻¹ ($P < 0.001$), which was lower than the control trial value ($P < 0.05$; Fig. 2C and Table 2). In parallel with the decline in cardiac output in the hyperthermic

trial, stroke volume and mean arterial pressure decreased from 136 ± 7 ml and 98 ± 1 mmHg at 10 min to a final value of 107 ± 6 ml and 89 ± 2 mmHg respectively ($P < 0.001$; Fig. 2D). During the same period HR increased from 143 ± 3 to 173 ± 5 beats min⁻¹ ($P < 0.001$; Fig. 2B), with the final value being 91.9 ± 2.0% of the subjects’ maximum heart rate. In the control trial, stroke volume, mean arterial blood pressure and HR were unchanged during the period from 10 to 60 min of exercise.

DISCUSSION

The main finding of the present study was that middle cerebral artery blood velocity was markedly reduced during prolonged exercise with hyperthermia. The reduction in MCA V_{mean} appears to be partly related to a hyperventilation-induced decline in arterial P_{CO_2} and

partly the consequence of reductions in cardiac output and blood pressure.

Hyperthermia-induced hyperventilation was observed in the present study in agreement with results obtained by Haldane (1905), Rowell *et al.* (1969), Cabanac & White (1995) and González-Alonso *et al.* (1998). As a consequence of the hyperventilation, arterial P_{CO_2} was reduced. This is clearly one of the main reasons for the reduction in MCA V_{mean} during exercise with hyperthermia, as arterial P_{CO_2} has a strong effect on the cerebral circulation, including MCA V_{mean} (Heistad & Kontos, 1983; Jørgensen, 1995). When individually determined regression lines for MCA V_{mean} and $P_{\text{a,CO}_2}$ obtained during exercise were used to attribute for the differences in $P_{\text{a,CO}_2}$ between the hyperthermic and control trial, it appeared that more than half of the reduction in MCA V_{mean} was related to the decline in $P_{\text{a,CO}_2}$. The hyperthermia-induced hyperventilation therefore has a clear detrimental effect on MCA V_{mean} , but the reason for the hyperventilation in hyperthermic humans is not clear. It may be that hyperventilation is a type of thermoregulatory panting (White & Cabanac, 1996) and it seems that a substantial fraction of the total cephalic heat loss can be liberated via this mechanism across a range of environmental conditions (Hanson, 1974; Rasch *et al.* 1991). Furthermore, heat loss from the upper respiratory tract may have a significant cooling effect on the brain (Mariak *et al.* 1999). Another explanation for the hyperventilation could be an increased feed-forward activation of the respiratory system as the effort to maintain the required α -motor output increases (Asmussen *et al.* 1965). In the hyperthermic trial, the subjects' rating of perceived exertion (Borg, 1975) increased in parallel with the increasing core temperature and heart rate (Table 1). Another possibility is that the small increase in anaerobic metabolism normally observed with hyperthermia (Dimri *et al.* 1980; González-Alonso *et al.* 1999a,b) stimulates ventilation in order to counteract acid-base disorders. However, the increased ventilation and the changes in cerebral circulation at the end of the hyperthermic trial are not simple consequences of differences in the environmental temperature, which is evidenced by the observation that \dot{V}_{E} and MCA V_{mean} were of similar magnitude at the beginning of exercise in both environments. Rather, stepwise multiple regression analysis identified core temperature as the best predictor of the increase in \dot{V}_{E} (Correlation coefficient, $r^2 = 0.99$; $P < 0.001$) and the decline in MCA V_{mean} ($r^2 = 0.99$; $P < 0.001$). Furthermore, MCA V_{mean} and \dot{V}_{E} were also highly correlated ($r^2 = 0.99$; $P < 0.001$), but \dot{V}_{E} did not increase the predicting power of the core temperature, because these two variables were tightly correlated. Although this type of statistical analysis has limitations, it provides a general description of the impact that the core temperature has on the pulmonary ventilation and the close association that these factors have with the cerebral circulation during exercise.

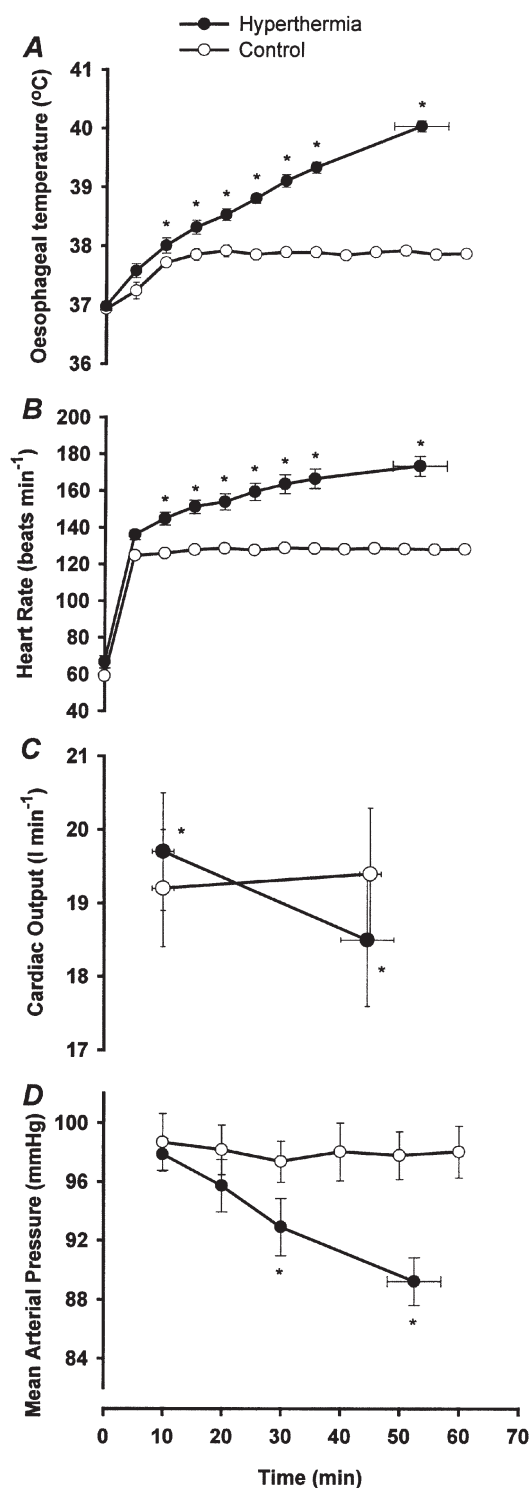


Figure 2. Oesophageal temperature, heart rate, cardiac output and mean arterial pressure responses during prolonged exercise with (○) and without (●) hyperthermia

A, oesophageal temperature during prolonged exercise; B, heart rate; C, cardiac output; D, mean arterial pressure. Values are means \pm S.E.M. for 8 subjects. * Significantly different from control, $P < 0.05$.

The part of the reduction in MCA V_{mean} that was not related to the decline in $P_{\text{a,CO}_2}$ may be explained by the reduction in cardiac output and arterial blood pressure. Using cardioselective β_1 -adrenergic blockade, Ide *et al.* (1998) showed that MCA V_{mean} is reduced when cardiac output and arterial blood pressure are attenuated during exercise with a large muscle mass. They concluded that MCA V_{mean} depends on cardiac output rather than blood pressure, and this seems to be an acceptable conclusion since mean arterial pressure both in the present study and in their study remained well within the cerebral autoregulatory range (Paulson *et al.* 1990). However, even within the autoregulatory range a small influence of reduced MAP on the cerebral circulation cannot be excluded (Heistad & Kontos, 1983). That blood flow to various tissue compartments can be reduced as a result of insufficient cardiac output is supported by the observations that reductions in cardiac output are accompanied by reduced leg blood flow both in dehydrated athletes (González-Alonso *et al.* 1998) and in patients with β -adrenergic blockade (Pawelczyk *et al.* 1992; Gullestad *et al.* 1993). Furthermore, patients with heart failure who are not able to increase cardiac output sufficiently have a lower MCA V_{mean} during dynamic exercise (Ide *et al.* 1999). In the present study, cardiac output was elevated at the beginning of exercise in the hyperthermic trial compared to control, thereby meeting the additional demand for blood flow to cutaneous areas (Rowell *et al.* 1969; Nielsen *et al.* 1990; Minson *et al.* 1998; González-Alonso *et al.* 2000). However, as hyperthermia developed, stroke volume was markedly reduced and due to the relatively smaller increase in heart rate, cardiac output was reduced by $1.2 \pm 0.2 \text{ l min}^{-1}$ at the end of exercise. Mechanisms underlying the decrease in stroke volume and alterations in cardiac output with different degrees of hyperthermia were recently discussed (González-Alonso *et al.* 2000). It seems reasonable to suggest that a decrease in stroke volume with severe hyperthermia might result from a reduction in both cardiac filling pressure and left-ventricular end-diastolic volume, due to the interaction of reduced central blood volume and increased skin blood flow, heart rate and temperature (Rowell *et al.* 1966; Fritzsche *et al.* 1999; González-Alonso *et al.* 2000).

A recent positron emission tomography (PET) study has shown that regional cerebral blood flow is sensitive to thermal stimulation (Craig *et al.* 2000), and an alternative possibility for the reduced MCA V_{mean} could be a temperature-induced redistribution of the cerebral blood flow. Core temperature and MCA V_{mean} are strongly correlated, but as discussed above it is reasonable to believe that the underlying causes of the decrease in MCA V_{mean} with hyperthermia are the hyperventilation-induced decrease in $P_{\text{a,CO}_2}$ and the impaired cardiac output.

It is important to understand to what extent the Doppler-determined MCA V_{mean} reflects volume flow. Some investigators (Poulin *et al.* 1999; Giller *et al.* 2000) have

determined a MCA blood flow index, which is derived from the intensity weighted mean flow velocity (V_{Iwmean}) multiplied by the total power of the Doppler spectrum. They found no significant change in MCA flow index during cycling and handgrip exercise, although there were increases in both V_{mean} and V_{Iwmean} during cycling. However, the measurement of V_{Iwmean} and the MCA flow index are dependent on a high quality Doppler signal, and would be expected to be affected more than V_{mean} by movement artefacts (Newell *et al.* 1994). Furthermore, Serrador *et al.* (2000) recently showed in a different experimental set-up that relative changes in MCA V_{mean} provide a good reflection of changes in MCA blood flow over a wide range of flow velocities, and they found no changes in MCA diameter during either hypercapnia or hyperventilation. Valdueza *et al.* (1997) also found no change in MCA diameter during hyperventilation. In accordance with this, the vasomotor response to $P_{\text{a,CO}_2}$ is restricted to the small vessels of the brain (Huber & Handa, 1967; Bradac *et al.* 1976) and the reduced $P_{\text{a,CO}_2}$ in the hyperthermic trial should not have any influence on the cross-sectional area of the proximal segment of the MCA. Furthermore, we recently measured the cross-sectional area of the MCA with magnetic resonance imaging (MRI) at rest and during handgrip exercise when subjects were normothermic (37.0°C) and when they were hyperthermic (39.3 – 39.5°C), and we found no temperature- or exercise-induced changes in MCA cross-sectional area (L. Nybo, M. Nowak, B. Nielsen & K. Thomsen, unpublished observations). Therefore, heat-induced dilatation of MCA does not seem to explain the reduction in MCA V_{mean} during the hyperthermic trial. Of course the possibility exists that combined hyperthermia and cycling elicit a different overall effect on the cross-sectional area of MCA than the one observed during resting hyperthermia and handgrip exercise, which is performed with a substantially smaller muscle mass. However, during exercise with a large muscle mass sympathetic activity normally increases with hyperthermia (González-Alonso *et al.* 2000) and this would have the opposite effect on MCA V_{mean} (Wahlgren *et al.* 1992).

Changes in MCA V_{mean} are not always a reflection of changes in whole-brain blood flow (Madsen *et al.* 1993; Jørgensen, 1995), but a fact that strongly supports the notion that total cerebral blood flow is reduced with hyperthermia during exercise is the marked decrease in $P_{\text{a,CO}_2}$ observed in the hyperthermic trial. Based on determinations of whole-brain blood flow 'CO₂ reactivity' (Reivich, 1964; Harper, 1965), it can be calculated that as a separate effect of declining $P_{\text{a,CO}_2}$, cerebral blood flow may be reduced by as much as 15 % ($\sim 5 \text{ mmHg}$ decline in $P_{\text{a,CO}_2}$ during the hyperthermic trial and a 'CO₂ reactivity' of 3 \% mmHg^{-1}) when severe hyperthermia is developed during exercise. Further evidence for reduced blood flow is provided by our recent observation of a 26 % increase in arterial–internal jugular venous O₂ difference during similar exercise and thermal stress as in the hyperthermic

trial in the present study (L. Nybo, M. Dalsgaard, B. Nielsen & N. Secher, unpublished observations). However, the present observations warrant further studies firstly to elucidate the effects of hyperthermia on the regional and global cerebral circulation, and secondly to investigate what consequences reduced cerebral blood flow might have on the metabolism and oxygenation of the brain during exercise with hyperthermia.

The present results may suggest that impaired cerebral circulation is involved in the early fatigue in the hyperthermic trial. The mechanism(s) by which hyperthermia causes fatigue during prolonged exercise in the heat is not well understood, but fatigue during moderate intensity exercise in the heat is closely associated with the attainment of critically high body temperatures (MacDougal *et al.* 1974; Nielsen *et al.* 1993; González-Alonso *et al.* 1999b), and fatigue within the central nervous system may be the underlying mechanism (Nielsen *et al.* 1993). Reduced cerebral blood flow during hyperthermia could support this hypothesis, but further evidence is needed. It should be mentioned that presyncopal symptoms (e.g. during orthostasis) are not observed until MCA V_{mean} is reduced to ~50% of the resting value (Jørgensen *et al.* 1993). However, 'central fatigue' during exercise with hyperthermia could be a consequence of reduced cerebral blood supply over a prolonged period of time.

In conclusion, middle cerebral artery blood velocity is markedly reduced during prolonged exercise with hyperthermia in humans. This reduction is partly related to a hyperventilation-induced decline in arterial P_{CO_2} and may be partly a consequence of a reduction in both cardiac output and arterial blood pressure.

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